

REMARKS/ARGUMENTS

Claims 91-105 are currently pending. Claims 91 and 104 are amended herein. Support for the amendment to Claim 91 to “a plant mismatch-directed endonuclease” is found at least on page 49, second paragraph “CEL I is a mismatch endonuclease isolated from celery”, i.e., a plant, and on page 48 “In addition to CEL I, a number of functionally equivalent, and potentially homologous activities found in extracts from a variety of plant species (Oleykowski, Nucleic Acids Res 1998;26:4597-602) may be used.”, and “Other mismatch-directed endonucleases such as ... SP nuclease (Oleykowski, Biochemistry 1999; 38: 2200-5) may be used.” Support for broadening the preamble of Claim 91 to more than linear sequence variants is found throughout the specification, for example in Example 5 and in original Claim 3. The amendment to Claim 104 corrects a typographical error.

Claims 66-72, 78-83, and 85 are canceled herein. While Applicants do not agree with the Examiner's rejections of these claims, in order to advance the prosecution of this application the claims have been canceled without prejudice toward the filing of the same or similar claims in a continuing application.

A Declaration from inventor Hal S. Padgett, Ph.D. is attached.

An Information Disclosure Statement is attached listing the articles referenced in this paper and in the Padgett declaration. Also listed in the IDS is the U.S. version of the Koltermann et al. PCT publication submitted in a previous IDS (8/3/2004). Applicants submit that the cited references taken alone or in combination neither anticipate nor render obvious the present invention. Consideration of the foregoing in relation to this application is respectfully requested.

DETAILED ACTION

Item 1: Applicants acknowledge the change in Examiner.

Item 4: Applicants acknowledge withdrawal of various rejections.

Claim Interpretation

Item 8: Applicants respectfully disagree with the Examiner's interpretation of "consisting essentially of" as equivalent to "comprising" in view of MPEP 2111 as there is a clear indication in the specification and claims of what the basic and novel characteristics actually are. However, in the interest of advancing prosecution of the application, Claim 91 has been amended to "comprising".

Item 9: Applicants respectfully disagree with the Examiner's interpretation of "cleaves at the mismatched nucleotides" as meaning cleavage at any distance from the nucleotide. However, in the interest of advancing prosecution of the application, Claim 91 has been amended to remove the phrase.

Claim Rejections – 35 USC § 102

Items 5, 7 and 12: Claims 67, 69-72, 85 and 87-90 were rejected under 35 U.S.C. 102(e) as allegedly anticipated by Vind. This rejection is moot, as the claims have been canceled.

Items 10-11: Claims 67, 69-72, 79, 80, 85 and 87-90 were rejected under 35 U.S.C. 102(b) as allegedly anticipated by Arnold et al. as evidenced by Lahue et al. This rejection is moot, as the claims have been canceled.

Claims Rejections – 35 USC § 103

Items 13-14: Claim 68 was rejected under 35 U.S.C 103(a) as allegedly unpatentable over Vind. This rejection is moot, as the claim has been canceled.

Item 15: Claim 68 was rejected under 35 U.S.C 103(a) as allegedly unpatentable over Arnold et al. as evidenced by Lahue et al. This rejection is moot, as the claim has been canceled.

Item 16: Claims 78 and 83 were rejected under 35 U.S.C 103(a) as allegedly unpatentable over Arnold et al. as evidenced by Lahue et al., Birkenkamp et al. and Youil et al. This rejection is moot, as the claims have been canceled.

Item 17: Claims 66 and 81 were rejected under 35 U.S.C 103(a) as allegedly unpatentable over Arnold et al. as evidenced by Lahue et al., Birkenkamp et al., Youil et al. and Oleykowski et al. This rejection is moot, as the claims have been canceled.

Item 18: Claim 82 was rejected under 35 U.S.C 103(a) as allegedly unpatentable over Arnold et al. as evidenced by Lahue et al., Birkenkamp et al., Youil et al. and Oleykowski et al. This rejection is moot, as the claim has been canceled.

Item 19: Claims 91, 93-96 and 98-105 were rejected under 35 U.S.C 103(a) as allegedly unpatentable over Arnold et al. as evidenced by Lahue et al. and Oleykowski et al. This rejection is traversed insofar as it might be applied to the claims as amended, as Applicants respectfully assert that the Examiner has not made a case for *prima facie* obviousness.

Arnold et al. teach a method for evolving a polynucleotide toward acquisition of a desired property by exposing a heteroduplex to a cellular DNA repair system to convert the heteroduplexes to parental polynucleotides or recombined polynucleotide variants. In one method the heteroduplexes are exposed to the host cells' DNA repair system *in vivo*. Arnold et al. also mention the possibility that a suitable DNA repair system could be prepared in the form of cellular extracts.

The Examiner asserts that Arnold et al. teach that cell extracts contain a mismatch recognizing and mismatch directed endonuclease that cleaves at the mismatched nucleotides. However, according to Lahue et al. the *E. coli* DNA repair system includes a protein that recognizes mismatches but does not cleave (Mut S), another protein that cleaves the DNA at a hemimethylated dGATC site, but does not recognize mismatches, and a protein to bridge these two. Other proteins in the *E. coli* repair system described by Lahue et al. include DNA helicase II and single-stranded DNA binding protein (SSB), Exonuclease I for removing large tracts of DNA that may include the mismatch, and the

DNA Pol III holoenzyme for resynthesizing the large tracts of DNA. From Table II of Cooper et al. (JBiolChem268(1993)11823) it is clear that purified MutH **does not** both recognize and cleave one strand at the site of the mismatch. None of these enzymes is a plant mismatch-directed endonuclease.

Furthermore, it would not be obvious to add a plant mismatch-directed endonuclease of the sort exemplified in the currently claimed method to a system that uses a DNA repair system. Since DNA repair systems have evolved to already be fully functional in repairing DNA and the enzymes act in a highly coordinated manner, and since the plant mismatch-directed endonucleases used in the currently claimed method of making sequence variants are not thought to be involved in cellular DNA repair systems, there would not be any motivation to add such an enzyme into a DNA repair system.

Indeed, in contemplating the mechanism of such cellular DNA repair systems, one of ordinary skill in the art would expect that addition of a plant mismatch-directed endonuclease of the type used in the presently claimed method to a DNA repair system would cause nicking of the heteroduplex at sites of mismatch such that when the DNA repair system started stripping away a strand of the duplex it might well start crossing places where the opposite strand had been nicked by the plant mismatch-directed endonuclease, resulting in double-strand breaks of the DNA and destruction of the molecule. Hence, one of ordinary skill in the art might expect the “plant mismatch-directed endonuclease” of the current method to be fundamentally incompatible with a cellular DNA repair system of the sort exemplified by Arnold et al., resulting in an inoperative invention or at least a reduction in recovered products. Indeed, Arnold et al. recommend **sealing** nicks **before** transforming the heteroduplex into *E. coli* as a way of increasing recombination.

In support of Applicants’ assertion that one of ordinary skill in the art at the time the invention would not have combined the cited references, the Padgett Declaration attached hereto describes some of the numerous publications available at the time of the instant invention that discuss the problems presented by unregulated nicking of heteroduplex molecules in the presence of a DNA repair system, involving the creation of double strand breaks and so destruction of the molecule. Further, work from Arnold’s laboratory presented in Volkov et al. NAR27(1999)e18 (cited in Applicants’ 6/13/2003

IDS) shows an understanding that nicks are a problem for their system in that they demonstrated that ligation of nicks (left over from creation of their heteroduplex) before transformation into *E. coli* lead to up to a 7-fold enhancement in recombination frequency (see Volkov page iii, last paragraph).

Oleykowski et al. teach a plant mismatch-directed endonuclease, but do not teach a method of making sequence variants as claimed in the instant application. The enzyme of Oleykowski et al. would not be used in the method of Arnold et al. for the reasons discussed above. Applicants respectfully submit that it would not have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the cited references.

As the cited references, alone or in combination, do not teach or suggest the claimed method, reconsideration and withdrawal of the rejection is respectfully requested.

Item 20: Claim 92 was rejected under 35 U.S.C 103(a) as allegedly unpatentable over Arnold et al. as evidenced by Lahue et al. and Oleykowski et al. This rejection is respectfully traversed. The deficiency of the cited references for making a *prima facie* case of obviousness is discussed above.

As the cited references, alone or in combination, do not teach or suggest the claimed method, reconsideration and withdrawal of the rejection is respectfully requested.

Item 21: Claim 97 was rejected under 35 U.S.C 103(a) as allegedly unpatentable over Arnold et al. as evidenced by Lahue et al. and Oleykowski et al. This rejection is respectfully traversed. The deficiency of the cited references for making a *prima facie* case of obviousness is discussed above.

As the cited references, alone or in combination, do not teach or suggest the claimed method, reconsideration and withdrawal of the rejection is respectfully requested.

Items 22-25: Double Patenting. Applicants respectfully request that resolution of obviousness-type double patenting matters be postponed until patentable subject matter is identified in the instant application.

In view of the amendments, Declaration and comments above, the rejections have been overcome with the exception of possible double patenting rejections.

Reconsideration and withdrawal of the rejections are respectfully requested. If any issues remain, including double patenting matters, the Examiner is encouraged to call the undersigned for prompt resolution.

If needed, Applicants petition for an extension of time sufficient for consideration of this response.

The commissioner hereby is authorized to charge payment of any fees under 37 CFR § 1.17, which may become due in connection with the instant application or credit any overpayment to Deposit Account No.504391.

Respectfully submitted,

/Wayne Fitzmaurice/

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Enclosures: Padgett Declaration 2
Information Disclosure Statement

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